Chapter 1

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia arising as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action or both (American Diabetes Association, 2010). It is a complex metabolic disorder of the endocrine system with dynamic expression of pathological disequilibria, resulting in various micro and macro vascular complications. It is characterized by high blood glucose levels (hyperglycaemia) due to the inability of the body’s cells to utilize glucose properly (West, 2000).

Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of populations in the world (Pareek et al., 2009). It is not a single disorder but a group of metabolic disorder characterized by chronic hyperglycaemia, resulting from insulin dysfunction. Increased thrust, increased hunger, increased urinary output, ketonemia and ketouria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat and protein metabolism. When ketone bodies present in the blood or urine, it is called ketoacidosis, hence proper care should be taken immediately, else it can leads to other diabetic complications (Craig et al., 2009).

1.1 Type of Diabetes mellitus

Diabetes mellitus can be devided in to two main types, Type 1, “Juvenile Diabetes mellitus” (Insulin Dependent Diabetes Mellitus, IDDM), and Type 2, “Adult type” (Non-Insulin Dependent Diabetes Mellitus, NIDDM) (Singh, 2011). Type 1 diabetes mellitus is characterized by a deficiency in endogenous insulin production mediated by an autoimmune process destroying the insulin-producing beta cells of the endocrine pancreas resulting in a dependency of exogenous insulin injections (Jacobsen et al., 2009) (Figure 1.1.1).This is the result of an ill-defined combination of genetic susceptibilities alongside environmental factors (Rowe et al., 2010).
Type 2 diabetes is generally viewed as a clinical syndrome with variable phenotypic expression rather than a single disease with a specific etiology. Phenotypic elements of the syndrome include cell insufficiency and insulin resistance. However, in most instances, the exact cause of type 2 diabetes seems to be polygenic in nature and is as yet unknown (Figure 1.1.2). Regardless of the primary causes of type 2 diabetes, a common clinical course is for patients to respond to therapy initially by normalizing their fasting glucose levels, but then to undergo gradual deterioration in glycaemic control despite optimal medical management using a variety of drugs (Robertson et al., 2004). Other type of diabetes is gestational diabetes which is mainly associated with pregnancy. Genetic defects of β-cell function or insulin action is also a type of diabetes mellitus commonly called maturity onset diabetes (Craig et al., 2009).

Neonatal diabetes mellitus is also a type of disorder in which insulin is required for the maintenance of blood glucose level in the first three months of life. It may be associated with intrauterine growth retardation and defects of chromosomes (Craig et al., 2009). Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterised by progressive non-autoimmune β cell failure (Craig et al., 2009). Cystic fibrosis related diabetes is primarily due to insulin deficiency, but insulin resistance during acute illness, secondary to infections and medications, may also contribute to impaired glucose tolerance and diabetes. Sometimes diabetes can also occur by other factors, like stress or in other case by the use of medication such as dexamethasone, L-asparaginase, glucocorticoids, cyclosporine or tacrolimus, olanzapine, risperidol, quetiapine and ziprasidone (Craig et al., 2009).
**Introduction**

**Figure 1.1.1** Schematic diagram of type-1 diabetes  

**Figure 1.1.2** Schematic diagram of type-2 diabetes  
1.2 Epidemiology of diabetes mellitus

The word ‘diabetes’ is derived from the Greek word “Diab” (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); ‘mellitus’ is the Latin word for “sweetened with honey” (refers to the presence of sugar in the urine). Greeks had a knowledge of a disease accompanied by polyurea and wasting of body glucose, whereas Aretaeus of Cappadocia mentioned a disease characterized by thirst and polyurea which was christened as Diabetes. Subsequently, the knowledge spread to Chinese, Iranians and Arabians. From the Middle East, the knowledge of DM had spread to Spain as a disease characterized by polyurea, polydipsia with sugary flavoured urine. With discovery of sugar in urine and its detection by laboratory test, the knowledge permeated into 18th century. Today, around 30 million people throughout the world suffer from DM. It is the most common metabolic abnormality in the world. Non-insulin dependent diabetes mellitus (NIDDM) is the most common form of diabetes constituting nearly 90% of the diabetic population in any country. Its prevalence varies in different geographic regions and also in different ethnic groups.

According to ancient Hindu physicians, ‘Madhumeha’ is a disease in which a patient passes sweet urine and exhibits sweetness all over the body, that is, in sweat, mucus, breath, blood, etc. They knew of the fact that the urine of a Madhumeha patient tastes sweet. They had recorded in their observations that - ‘if too many ants swarm around a spot of urine (Singh, 2011).

The Asia-Pacific region contains some of the most populous countries in the world. The largest country, China, contains 20% of the world’s population (1.2 billion). Asia also contains the world’s second largest country, India, with a population of 1 billion and fourth largest country, Indonesia, with a population of about 200 million. Thus, the Asia-Pacific region is of prime importance to the epidemiology of diabetes. The region combines a high proportion of the world’s population with rapidly rising diabetes prevalence rates. The Western Pacific region, along with the Indian subcontinent, is at the forefront of the current epidemic of type 2 diabetes mellitus. In 1998 it was estimated that, globally, there were already 140 million people with diabetes. Predictions compiled by Dr Hilary King of the World
Health Organization (WHO) indicate that this figure will rise to 300 million by the year 2025. Of these, more than 150 million will be in Asia. The figures for India are predicted to rise from an estimated 15 million in 1995 to 57 million in 2025. For China, current estimates are 15 to 20 million, with a predicted rise to 50 million by 2025. Thus, more than 30% of the global number of people with diabetes in 2025 will be in these two countries alone (King, 1999).

1.3 Major complications associated with diabetes

One of the characteristics of diabetes mellitus is that it is associated with a large number of other diseases. Generally, the injurious effects of hyperglycaemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).

1.3.1 Microvascular complications of diabetes

1.3.1.1 Diabetic retinopathy

Diabetes is an important cause of impaired vision. The World Health Organization estimates that diabetic retinopathy is the cause of blindness in 5% of blind people worldwide (Resnikoff et al., 2002). It is an ocular manifestation of diabetes, a systemic disease, which affects up to 80 percent of all patients who have had diabetes for 10 years or more. Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there was proper and vigilant treatment and monitoring of the eyes. The longer a person has diabetes, the higher his or her chances of developing diabetic retinopathy (Falcao et al., 2010) and severity of retinopathy was related to longer duration, high levels of glycosylated hemoglobin, presence of proteinuria, higher diastolic BP, and male sex (Klein et al., 1984).
1.3.1.2 Diabetic nephropathy

Although it takes years of living with diabetes to develop severe kidney problems, a significant fraction of patients with diabetes will have a life-threatening encounter with renal disease. About half of patients with diabetes develop microalbuminuria at some point. Approximately one third will progress to proteinuria, one third will remain microalbuminuric and one third will revert to normal albumin excretion (Boulton et al., 2005). Microalbuminuria and proteinuria are more common in ethnic minorities worldwide (Schrijvers et al., 2004; Brownlee, 2004). Diabetic nephropathy (DN), a devastating late complication of Type 1 diabetes, is characterized by increased arterial blood pressure, progressive proteinuria, a relentless decline in renal function and up to a 37-fold increased risk of cardiovascular death (Saraheimo et al., 2003).

1.3.1.3 Diabetic neuropathy

There are three types of nerve disease: peripheral, autonomic, and mononeuropathy. Peripheral neuropathy affects the hands, feet, legs, toes, or fingers. A person's feet, legs, and fingertips may lose feeling, burn, or become painful (Park et al., 2004). In patients with neuropathy (which diminishes sensation leading to unawareness of injury or pain) or macrovascular damage, a minor bruise or cut, large calluses or improper toe nail cutting can lead to skin ulcers, infections, gangrene or even amputation. Another type of nerve disease that may occur after several years of diabetes is called autonomic neuropathy. Autonomic neuropathy affects the internal organs such as the heart, stomach, sexual organs, and urinary tract. It can cause digestive problems and lead to incontinence (a loss of ability to control urine or bowel movements), and sexual impotence (Ewing et al., 1980). Mononeuropathy is a form of nerve disease that affects specific nerves, most often in the torso, leg, or head. Mononeuropathy may cause pain in the lower back, chest, abdomen, or in the front of one thigh. Sometimes, this nerve disease can cause aching in the eye, an inability to focus the eye, or double vision. Mononeuropathy may also cause facial paralysis, Bell's palsy, or problems with hearing (Zochodne et al., 1995). The prevalence of neuropathy among diabetic patients is uncertain. This is partly due to
the variety of different criteria which are used to diagnose neuropathy. Despite this uncertainty, it appears that the prevalence of neuropathy is dependent primarily on the duration and severity of hyperglycaemia in both IDDM and NIDDM. In the case of IDDM, it usually does not appear until five years after the onset of the disease and it ultimately affects up to 50% of all patients with diabetes (Lluch et al., 1998).

1.3.2 Macrovascular complication of diabetes

Macrovascular disease (MVD), especially coronary heart disease, is the most common cause of mortality in Type 2 diabetes (Kirkman et al., 2006). Macrovascular complications, which manifest in about 80 percent of patients with type 2 diabetes mellitus (type 2 DM), are a leading cause of morbidity and mortality worldwide (Zargar et al., 1999). The group with macrovascular complications included patients with coronary artery disease (CAD), peripheral vascular disease (PVD) and cerebrovascular disease (CVD) (Saxena et al., 2005). Diabetes is associated with a number of macrovascular risk factors, including obesity, hypertension, and dyslipidemia. However, the risk for MVD remains independently associated with diabetes, even when controlling for other known risk factors (Haffner et al., 1998).

Diabetes has also been implicated as the underlying cause of macrovascular complications such as acute myocardial infarction (AMI), angina pectoris, ischemic stroke, and transient ischemic attacks. Evidence has shown that people with diabetes are two to four times more likely to die from heart disease or suffer a stroke (Vinik and Flemmer, 2002). Many reports have shown that inflammation and disorder of immunity were closely related to insulin signal, insulin resistance and endothelial cell dysfunction, resulting in the development of atherosclerotic macrovascular and coronary heart diseases (Shi et al., 2013).

1.4 Cause of Diabetes mellitus

The causes of diabetes depend on the type of diabetes. Type 1 occurs mainly due to β-cell destruction, mediated through either immune mediated or idiopathic, whereas Type 2 diabetes occurs mainly due to insulin resistance or with relative
insulin deficiency. Diabetes is also associated with life style factors and genetics (Craig et al., 2009).

There are various types of other factors that involved in the development of diabetes which are the genetic material such as chromosomal and mitochondrial DNA mutation, Leprechaunism, Rabsonmendenhall syndrome and lipoatrophic diabetes is associated with the genetic defects in insulin action. In some cases congenital rubella and cytomegalovirus infection also lead to the cause of diabetes mellitus. Sometimes drugs and other chemicals such as pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, β- adrenergic agonists, thiazides, α- interferon can cause diabetes mellitus. Abnormalities in such as pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, fibrocalculous, pancreatopathy can also develop diabetes. There are other factors related to immune system such as ‘Stiff- man’ syndrome and anti-insulin receptor antibodies that are involved in the development of the diabetes. Disease associated with pancrease such as aromeguly, cushing’s syndrome, glucagonoma, phaeochromocytomes, hyperthyroidism and aldosteronoma can also mediate diabetes mellitus. There are some other genetic syndromes such as Down syndrome, Klinsfelter syndrome, Turner syndrome, Wolfram, Friedreich’s ataxia, Huntington’s chorea, Laurence- Moon- Biedl syndrome, Myotonic dystrophy, Prader–Willi syndrome which were also involved in the development of diabetes in some cases (Craig et al., 2009).

1.5 Diagnostic feature of diabetes mellitus

Elevated blood glucose level and the presence and absence of symptoms such as polyuria, polydipsia and polyphagia in association with glycosuria and ketouria are the main diagnostic criteria of diabetes. Diabetes mellitus can be confirmed by estimation of blood glucose level. The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued monitoring and observation with fasting or 2 hour post-prandial blood glucose levels and an oral glucose tolerance test (OGTT). Symptoms of diabetes plus plasma glucose concentration ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl and 2-hours post
load glucose ≥ 200 mg/dl during an OGTT are considered as diabetes (Singh, 2011, Craig et al., 2009). Sometimes measurement of specific antibody markers such as islet cell antibody (ICA), GAD, IA₂, IAA and HbA₁c may be helpful for the diagnosis of diabetes mellitus. Measurement of fasting insulin and C-peptide level can also be useful in the diagnosis of type 2 diabetes in children (Craig et al., 2009).

Figure 1.5.1 Symptoms of diabetes
Source: http://blog.docsuggest.com/615/diabetes-mellitus-not-so-sweet-after-all/

1.6 Available therapy for diabetes mellitus

The treatment of diabetes mellitus is considered as the main global problem and successful treatment has yet to be discovered. Even though insulin therapy and oral hypoglycaemic agents are the first line of treatment for the diabetes mellitus they
have some side effect and fail to significantly alter the course of diabetes (Venkatesh et al., 2010).

1.6.1 Human insulin

Human insulin is a polypeptide, having a molecular weight of about 6000 Da, consisted of two amino acid chains A and B, which are linked by two disulphide (-S-S-) linkage. Normal human pancreas contains about 8-10 mg. of insulin. Insulin is not suitable for oral administration due to inactivation by digestive enzyme. 80% of exerted insulin is normally degraded in the liver and kidneys. The amount of insulin secreted per day in a normal human is about 40 units. The dose of insulin required to control the diabetes varies from patient to patient and from time to time in the same patient (Singh, 2011).

![Figure 1.6.1.1 Schematic diagram of insulin mechanism against hyperglycaemia](http://www.medbio.info/horn/time%203-4/insulin's%20mechanism%20of%20action.htm)

1.6.2 Oral hypoglycaemic drugs

Oral hypoglycaemic drugs are used only in the treatment of type 2 diabetes which is a disorder involving resistance to secreted insulin. Type 1 diabetes involves
a lack of insulin and requires insulin for treatment. There are now four classes of hypoglycaemic drugs.

1.6.2.1 Sulfonylureas

Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes and appear to function by stimulating insulin secretion. The net effect is increased responsiveness of β-cells (insulin secreting cells located in the pancreas) to both glucose and non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal. Sulfonylureas are usually well tolerated. Hypoglycaemia is the most common side effect and is more common with long-acting sulfonylureas (Lorenzati et al., 2010).

1.6.2.2 Repaglinide

Repaglinide is an antidiabetic drug in the class of medications known as meglitinides, and was invented in 1983. It is sold by Novo Nordisk under the name of Prandin in the U.S., GlucoNorm in Canada, Surepost in Japan, Repaglinide in Egypt by EIPICO, and NovoNorm elsewhere. Repaglinide is a short-acting glucose-lowering drug recently approved by the Food and Drug Administration for therapy of type 2 diabetes alone or in combination with metformin. It is structurally different than sulfonylureas, but acts similarly by increasing insulin secretion (Lorenzati et al., 2010).

1.6.2.3 Natiglinide

Natiglinide (Starlix) is a very short-acting glucose lowering drug whose mode of action is similar to the sulfonylureas and is nearing approval by the FDA. A potential advantage of this drug is that it seems to have its effect on the first phase of insulin release rather than the late phase of insulin release. The first phase of insulin release is brisk, of short duration and occurs within minutes of ingesting food. It is this first phase of insulin release that is abnormal in early diabetes & can often be
found in patients with impaired glucose tolerance prior to the onset of diabetes. The usual dose is 120 mg before meals (Lorenzati et al., 2010).

1.6.2.4 Metformin

Metformin has been used in Europe for over thirty years, and has been available in the United States since March 1995. It is effective only in the presence of insulin but, in contrast to sulfonylureas, it does not directly stimulate insulin secretion. Its major effect is to increase insulin action.

How metformin increases insulin action is not known but it is known to affect many tissues. One important effect appears to be suppression of glucose output from the liver. The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and diarrhea. These symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug (Lorenzati et al., 2010). Continuous metformin therapy throughout pregnancy in women with PCOS (polycystic ovary syndrome) improves pregnancy outcomes by decreasing spontaneous miscarriage rates and prevention of gestational diabetes mellitus with its co morbidity and mortality (Abd El Hameed et al., 2011).

1.6.2.5 Thiazolidinediones

The thiazolidinediones such as Avandia (Rosiglitazone) and Actos (Pioglitazone) reverse insulin resistance by acting on muscle, fat and to a lesser extent liver to increase glucose utilization and diminish glucose production. The mechanism by which the thiazolidinediones increase insulin action is not well understood but they may be acting by redistributing fat from the visceral compartment to the subcutaneous compartment. We know that visceral fat is associated with insulin resistance (Lorenzati et al., 2010).
1.6.2.6 Alpha-glucosidase inhibitors

The $\alpha$-glucosidase inhibitors include acarbose (Precose) & Miglitol (Glycet) and are available in the United States. They inhibit the upper gastrointestinal enzyme that converts dietary starch and other complex carbohydrates into simple sugars which can be absorbed. The result is to slow the absorption of glucose after meals.

As in patients with type 2 diabetes, patients with type 1 diabetes have a reduction in the amplitude of glucose excursion and HbA1c and a possible reduction in nocturnal hypoglycaemia with alpha-glucosidase inhibitors. The main side effects of alpha-glucosidase inhibitors are flatulence and diarrhea. These symptoms are usually mild and do not necessitate cessation of therapy (Lorenzati et al., 2010).

1.7 Oxidative stress and diabetes

The condition of imbalance between regeneration of free radicals and defence mechanism in the body is called as oxidative stress. Role of oxidative stress in development and progression of diabetes has been reported in many studies (Uttara et al., 2009; Rahimi et al., 2005). Hyperglycaemia itself has been documented as reason of prevalence of oxidative stress (Dungan et al., 2009).

Oxidative stress is deleterious in many aspects to the cellular molecules. It oxidized nucleic acids, lipids, proteins and thus alters their status and functions. Lipids and proteins are the major structural biomolecules in the body. Damage to them impairs several biophysical properties of the cell including malfunctioned fluidity of membranes due to disturbed deformity (Haliwell and Gutteridge, 2007; Pandey et al., 2010). Peroxidation of lipids produces highly reactive byproducts including malondialdehyde (MDA), acrolein, 4-hydroxynonenal (HNE), 4-oxononenal (ONE), and isolevuglandins (IsoLGs) (Guo et al., 2012). Significant changes in lipid metabolism and structure have been reported in diabetes, particularly in patients with vascular complications (Fowler, 2008). Increased lipid peroxidation in diabetics has been reported in most of the studies (Saddala et al., 2013).
Protein acts as the functional molecule of the cells. Oxidation of proteins influences the biochemical pathways, physiology and signalling adversely. Protein carbonyls and advanced oxidation protein products (AOPPs) are the oxidation product of proteins and are considered as the potent marker of oxidative stress (Pandey and Rizvi, 2010; Niki, 2009). Oxidative stress in diabetics leads to increased oxidation of proteins which leads to development of severe diabetic complications (Pandey et al., 2010; Piwowar et al., 2007). Depleted levels of inherent defensive molecules against oxidative stress have also been characterised during type 2 diabetes mellitus. Glutathione (GSH), an efficient antioxidant present in almost all living cells, is known as a biomarker of redox imbalance at cellular level (Pandey and Rizvi, 2011). Under oxidative conditions GSH is reversibly oxidized to glutathione disulfide (GSSG) (Zhu et al., 2006). Reduced glutathione level in tissue has often been considered to be indicative of increased oxidative stress in diabetes and may be one of the factors in the oxidative DNA damage in type 2 diabetics (McLennan et al., 1991; Makni et al., 2011).

Malfunctioned enzymatic antioxidant defence machinery is a key feature in diabetic peoples. An array of experimental evidence suggests the impairment in the enzymes associated in anti-oxidative defence in diabetic mellitus (Rashid et al., 2013). Catalase (CAT), one of the main enzyme in this system enzymatically process deleterious hydrogen peroxide into oxygen and water. Increased frequency of diabetes has been documented in patients with CAT deficiency which leads, in the β-cell, to an increase in oxidative stress and, ultimately, to a failure of this cell type. β-cells are rich in mitochondria and that this organelle might be a source of ROS (Goth and Eaton, 2000). Superoxide dismutases (SOD) catalyse the dismutation of superoxide anion (O$_2^-$) into H$_2$O$_2$ and molecular oxygen (Faraci and Didion, 2004). Impaired activity of SOD of diabetes during oxidative stress and diabetes indicates the pivotal role of oxidative stress in type 2 diabetes which is responsible for the onset of many late complications of diabetes such as kidney and neuronal problems.

1.8 Role of herbal remedies in diabetes mellitus
In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Sushruta. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information reports that about 800 plants may possess anti-diabetic potential (Patil et al., 2011). Plant derivatives with purported hypoglycaemic properties have been used in folk medicine and traditional healing systems around the world. Many modern pharmaceuticals used in conventional medicine today also have natural plant origins. Among them, metformin was derived from the flowering plant, Galega officinalis, which was a common traditional remedy for diabetes. Similarly, the use of vitamin and mineral supplements for primary or secondary disease prevention is of increasing interest (Yeh et al., 2003).

Plants are a rich source of antioxidants and have a great potential to act as a defence to the free radical attack. These plants contain bioactive compounds known as phytochemicals that work along with essential nutrients and dietary fibre to protect against diseases. Originally, plants produce these compounds for self protection whereas recent studies establish the defensive role of these phytochemicals against human diseases as well. These compounds are prevalent in almost all parts of plant and have the potential to reduce risk of various diseases through their multidimensional properties (Atale et al., 2011). Plants have inorganic macro and microelements such as vanadium, zinc, chromium, copper, iron, potassium, sodium, and nickel which plays an important role in the maintenance of normoglycaemia by activating the β-cells of the pancreas (Narendhirakannan et al., 2005).

1.9 Composite formulation of herbal plants for treatment of diabetes

In the traditional system of Indian medicine, plant formulation and combined extracts of plants are used as drug of choice rather than individual. Diasulin, a combination of ten herbal plants exert a significant antihyperlipidemic and
antiperoxidative effect. This could be due to different types of active principles, each with a single or a diverse range of biological activities, which serves as a good adjuvant in the present armamentarium of antidiabetic drug (Saravanan and Pari, 2005). Dihar is a combination of 8 herbal medicinal plants exerts a significant antidiabetic, antihyperlipidemic and antioxidant effect. This could be due to different type of active principles from various plants, which may have different mechanisms of action therefore combination may be beneficial (Patel et al., 2009).

Objectives

In view of medicinal properties of plant, the present study was conducted to investigate the antidiabetic, antihyperlipidemic and antioxidant activities of methanolic composite extract in alloxan induced diabetic wister rats.

Since, diabetic manifestations involve free radical associated damage, it has been hypothesized that, a combination of the five identified plants, Murraya koenigii, Azadirachta indica, Ocimum sanctum, Aegle marmelos leaves and Syzygium cumini fruits, can effectively target both, metabolic dysregulation and oxidative stress, associated with diabetic manifestations and be a better treatment paradigm than either alone. The study has comprised with the following objectives:

1- Phytochemical screening and evaluate the antioxidant status of Murraya koenigii, Azadirachta indica, Ocimum sanctum, Aegle marmelos leaves, Syzygium cumini fruits and composite extract.

2- To determine the effect of methanolic composite extracts on body weight, blood glucose level of Wistar rats in different time intervals.

3- Antidiabetic, antihyperlipidemic and antioxidant effect of methanolic composite extracts on blood of Wistar rats.

4- To determine the effect of methanolic composite extracts on Protein, Protein carbonyl and antioxidant (enzymic & nonenzymic) in liver and brain of Wistar rats.